REMARKS

Claims 2-9, 12-19 and 36-42 are canceled without prejudice. Claim 1 has been amended. Claims 43-70 have been added. Thus after entry of the instant amendment, Claims 1 and 43-70 are pending. A marked up copy of the amended claim is attached at Exhibit A. For the Examiner's convenience, a clean copy of all pending claims after entry of the instant amendment is attached at Exhibit B.

Applicants reserve the right to prosecute any canceled subject matter in one or more continuation, divisional or continuation-in-part applications.

I. THE AMENDMENT OF THE CLAIMS

Claim 1 has been amended to recite an ApoA-I agonist compound (i) comprising a 15 to 29-residue peptide comprising formula (I); or (ii) a 15 to 26-residue deleted peptide or peptide analogue according to formula (I) in which one or two helical turns are optionally deleted. Support for Claim 1 may be found, for example, in Claims 1, 10, 11 and 15 as originally filed and in the specification, for example, at page 50, line 27 to page 51, line 22.

New Claim 43 recites a 15 to 26-residue deleted peptide or peptide analogue of Claim 1 in which one helical turn is deleted. Support for new Claim 43 may be found in the specification, for example, at page 50, lines 11 to 19 and page 51, lines 1 to 13.

New Claim 44 recites a 15 to 26-residue deleted peptide or peptide analogue of Claim 1 in which three, four, six, seven or eight residues X_1 to X_{22} are deleted. Support for new Claim 44 may be found, for example, in Claim 1 as originally filed and in the specification, for example, at page 51, lines 1 to 13.

New Claims 45 and 46 recite 15 to 26-residue deleted peptide or peptide analogues in which 3 and 4 consecutive residues are deleted, respectively. Support for new Claims 45 and 46 may be found in the specification, for example, at page 51, lines 1 to 13.

New Claims 47 and 48 recite 15 to 26-residue deleted peptide or peptide analogues in which two non-contiguous sets of 3 or 4 consecutive residues are deleted, respectively. Support for new Claims 47 and 48 may be found in the specification, for example, at page 51, lines 1 to 13.

New Claim 49 recites a 15 to 26-residue deleted peptide or peptide analogue in which one set of 3 consecutive residues and one set of 4 consecutive residues are deleted. Support for new Claim 49 may be found in the specification, for example, at page 51, lines 1 to 13.

New Claim 50 recites a 15 to 26-residue deleted peptide or peptide analogue in which 6, 7 or 8 consecutive residues are deleted. Support for new Claim 50 may be found in the specification, for example, at page 51, lines 1 to 13.

New Claims 51 and 52 recite 15 to 26-residue deleted peptide or peptide analogues in which residues 18, 19, 20 and 22 and 3, 6, 9 and 10 are not deleted, respectively. Support for new Claims 51 and 52 may be found in the specification, for example, at page 51, lines 14 to 22.

New Claim 53 recites a 15 to 26-residue deleted peptide or peptide analogue in which X_{23} is absent. Support for new Claim 53 may be found, for example, in Claim 1 as originally filed.

New Claim 54 recites a 15 to 26-residue deleted peptide or peptide analogue in which the "-" between residues designates -C (O) NH- , Z_1 is H_2N- , and Z_2 is -C (O) OH or a salt thereof. Support for new Claim 54 may be found, for example, in Claim 13 as originally filed.

New Claims 55 and 56 recite 15 to 26-residue deleted peptide or peptide analogues in which the mean hydrophobic moment, $<\mu_H>$, is about 0.45 to about 0.65 and about 0.50 to about 0.60, respectively. Support for new Claims 55 and 56 may be found in the specification, for example, at page 31, lines 1 to 10.

New Claims 57 and 58 recite 15 to 26-residue deleted peptide or peptide analogues in which the mean hydrophobicity, $<H_o>$, is about -0.050 to about -0.070, and about -0.030 to about -0.055, respectively. Support for new Claims 57 and 58 may be found in the specification, for example, at page 31, lines 11 to 24.

New Claims 59 and 60 recite 15 to 26-residue deleted peptide or peptide analogues in which the mean hydrophobicity of the hydrophobic face, $<H_o^{pho}>$, is about 0.90 to about 1.20 and about 0.94 to about 1.10, respectively. Support for new Claims 59 and 60 may be found in the specification, for example, at page 31, line 25 to page 32, line 8.

New Claims 61 and 62 recite 15 to 26-residue deleted peptide or peptide analogues in which the pho angle is about 160° to about 220° and about 180° to about 200°, respectively.

Support for new Claims 61 and 62 may be found in the specification, for example, at page 32, line 9 to page 33, line 2.

New Claims 63, 64 and 65 recite ApoA-I agonist-lipid complexes comprising various ApoA-I agonist compounds and a lipid. Support for new Claims 63, 64 and 65 may be found in the specification, for example, at page 79, line 18 to page 83, line 28.

New Claims 66, 67 and 68 recite various pharmaceutical compositions of ApoA-I agonist compounds and lipids. Support for new Claims 66, 67 and 68 may be found, for example, in Claim 36 as originally filed and in the specification, for example, at page 79, line 18 to page 83, line 28.

New Claims 69 and 70 recite pharmaceutical compositions in the form of a lyophilized powder and solution. Support for new Claims 69 and 70 may be found, for example, in Claims 34 and 35 as originally filed and in the specification, for example, at page 79, line 18 to page 83, line 28.

As the amendment and new Claims are fully supported by the specification and Claims as originally filed; they do not constitute new matter. Entry thereof is respectfully requested.

II. CLAIM OBJECTIONS

Claims 1-13 and 36-42 stand objected to for alleged informalities. Claim 1 has been amended to correct minor errors in claim language. Claims 2-9, 12-19 and 36-42 have been canceled thereby rendering the rejection of these claims moot. Applicants respectfully request that the objections to Claims 1-13 and 36-42 be withdrawn.

III. CLAIM REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-9, 12-17 and 36 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite. Claim 1 has been amended to correct minor errors in claim language.

Amended Claim 1 recites an ApoA-I agonist compound comprising formula (I) comprising Z_2 in which Z_2 is -C (O) NRR or -C (O) OR; and each R is independently -H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl or a 1 to 7-residue peptide or peptide analogue in

which one more bonds between residues 1-7 are independently a substituted amide, an isostere of an amide or an amide mimetic. Applicants therefore submit that amended Claim 1 is definite as to Z_2.

Amended Claim 1 recites an ApoA-I agonist compound comprising formula (I) in which each "-" between residues X_1 to X_{23} and between residues of the peptide to Z_2 independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic. Applicants therefore submit that amended Claim 1 is definite as to X_1 to X_{23} and Z_2.

Claims 4, 6 and 9 have been canceled thereby rendering rejection of these claims moot.

Applicants respectfully request that the rejection of Claims 1-9, 12-17 and 36 under 35 U.S.C. §112, second paragraph be withdrawn.

IV. CLAIM REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-13 and 36-42 stand rejected under 35 U.S.C. §112, first paragraph as allegedly not being enabled. Claims 2-13 and 36-42 have been canceled thereby rendering rejection of these claims moot.

The Examiner asserts that the specification does not enable one of ordinary skill in the art to delete residues while maintaining the amphipathic α-helical motif. Applicants submit that Claim 1 as originally filed, is fully enabled by the specification. Nevertheless, merely to expedite prosecution and secure rapid allowance of the claims, Claim 1 has been amended.

Applicants submit that amended Claim 1 and new Claims 43 to 62 are fully enabled by the specification as originally filed. Amended Claim 1 recites an ApoA-I agonist compound comprising (i) a 15 to 29-residue peptide comprising formula (I) or (ii) a 15 to 26-residue deleted peptide or peptide analogue according to formula (I) in which one or two helical turns of the peptide are optionally deleted.

A claim is enabled if one of skill in the art, guided by Applicant's disclosure, can make and use the claimed invention without undue experimentation. *See Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916); *In re Wands*, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The test is not whether any experimentation is necessary, but whether, if

experimentation is necessary, it is not undue. *See In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976).

Applicants submit that Claim 1 is enabled because the specification teaches one of skill in the art how to make and use the deleted peptide and peptide analogues without undue experimentation. For example, the specification teaches that biological activity of the peptides correlates with amphipathic α-helical structure. The specification further teaches one of skill in the art how to make and use the peptide and peptide analogues of formula (I) wherein one or two helical turns are deleted while maintaining the amphipathic α-helical structure and activity of the resultant peptide. In particular, the specification teaches that an α-helix contains 3.6 residues per turn, thus allowing for 3 to 4 residues to be deleted depending upon the position within the helix of the first residue to be deleted. (Page 51, lines 1 to 13). One of skill in the art will recognize that deletion of more than one helical turn can be accomplished by deleting contiguous or non-contiguous sets of 3 or 4 consecutive amino acid residues to achieve deleted peptides containing as few as 18 or even 15 amino acid residues. The specification further teaches two preferred embodiments; one in which residues 18, 19, 20 and 22 are not deleted and another in which residues 3, 6, 9 and 10 are not deleted. (Page 51, lines 14 to 22). Thus, deletions of one or two helical turns are fully enabled in the specification as originally filed.

In addition, the specification also teaches one of skill in the art the structural and/or physical properties that are important for activity of the deleted peptide and peptide analogues. For example, a feature of the ApoA-I peptides of formula (I) is their ability to form amphipathic α-helices in the presence of lipids. Properties important for activity of the α-helices are clearly taught in the specification, including for example: degree of amphipathicity, overall hydrophobicity, mean hydrophobicity, hydrophobic and hydrophilic angles, hydrophobic moment, mean hydrophobic moment, and net charge of the α-helix. (Page 30, lines 16 to 23). The calculation of these properties are taught extensively in the specification. For example, the net amphipathicities of peptides of different lengths can be directly compared by way of the mean hydrophobic moment, $<\mu_H>$; calculated by dividing the hydrophobic moment, μ_H, of the helix by the number of residues in the peptide. (Page 30, line 24 to page 31, line 10). Likewise, the specification teaches calculation of the mean hydrophobicity of the hydrophobic face, $<H_o^{pho}>$; obtained by dividing the sum of the

hydrophobicities of each amino acid residue in the peptide by the number of amino acid residues. (Page 31, line 11 to page 32, line 8).

Thus, the specification teaches deletion of individual residues, particularly those resulting in deletion of a full α-helical turn. Furthermore, the specification teaches the structural and/or physical properties of the deleted peptide and peptide analogues and how those values are calculated. Therefore, the specification teaches one of skill in the art to make and use the deleted peptide and peptide analogues without undue experimentation.

Applicants respectfully submit that amended Claim 1 and new Claims 43-70 are fully enabled. Applicants further request that the rejection of Claims 1-13 and 36-42 under 35 U.S.C. §112, first paragraph be withdrawn.

V. DOUBLE PATENTING

Claims 1-13, 36-42 stand rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over U.S. Patent Nos. 6,004,925, 6,037,323 and 6,265,377. Applicants submit herewith a Terminal Disclaimer and fee and respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants submit that Claims 1 and 43-70 satisfy all the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly solicited.

No fee is believed due in connection with this response. However, pursuant to 37 C.F.R. §1.136 (a)(3), the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. §1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds LLP, U.S. Deposit Account No. 16-1150 (Order No. 9196-018-999).

Respectfully submitted,

Date: February 26, 2002

42,983

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EXHIBIT A

Claim Amendments: Marked Up Copy

1. (Twice amended) An ApoA-I agonist compound comprising:

(i) a [16] 15 to 29-residue peptide or peptide analogue which forms an amphipathic α-helix in the presence of lipids and which comprises [the structural] formula (I) :

$$Z_1\text{-}X_1\text{-}X_2\text{-}X_3\text{-}X_4\text{-}X_5\text{-}X_6\text{-}X_7\text{-}X_8\text{-}X_9\text{-}X_{10}\text{-}X_{11}\text{-}X_{12}\text{-}X_{13}\text{-}X_{14}\text{-}X_{15}\text{-}X_{16}\text{-}X_{17}\text{-}X_{18}\text{-}X_{19}\text{-}X_{20}\text{-}X_{21}\text{-}X_{22}\text{-}X_{23}\text{-}Z_2$$

or a pharmaceutically acceptable salt thereof, wherein:

X_1 is Pro (P), Ala (A), Gly (G), Gln (Q), Asn (N), Asp (D) or D-Pro (p);

X_2 is an aliphatic residue;

X_3 is a Leu (L) or Phe (F);

X_4 is Glu (E)

X_5 is an aliphatic residue;

X_6 is Leu (L) or Phe (F);

X_7 is Glu (E) or Leu (L);

X_8 is Asn (N) or Gln (Q);

X_9 is Leu (L);

X_{10} is Leu (L), Trp (W) or Gly (G);

X_{11} is an acidic residue;

X_{12} is Arg (R);

X_{13} is Leu (L) or Gly (G);

X_{14} is Leu (L), Phe (F) or Gly (G);

X_{15} is Asp (D);

X_{16} is Ala (A);

X_{17} is Leu (L);

X_{18} is Asn (N) or Gln (Q);

X_{19} is a basic residue;

X_{20} is a basic residue;

X_{21} is Leu (L);

X_{22} is a basic residue;

X_{23} is absent or a basic residue;

Z_1 is [H_2N-] R_2N- or [RC(O)NH-] RC(O)NR-;

Z_2 is -C (O) NRR[,] or -C (O) OR [or -C(O)OH or a salt thereof];

each R is independently -H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl or a 1 to 7-residue peptide or peptide analogue in which one more bonds between residues 1-7 are independently a substituted amide, an isostere of an amide or an amide mimetic;

each "-" between residues [X_n] X_1 to X_{23} and between residues of the peptide to Z_2 independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic; or

(ii) a 15 to 26-residue deleted [from] peptide or peptide analogue according to [of structural] formula (I) in which [at least one and up to eight of residues X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , X_8 , X_9 , X_{10} , X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , X_{16} , X_{17} , X_{18} , X_{19} , X_{20}, X_{21} and X_{22} are deleted] one or two helical turns of the peptide or peptide analogue are optionally deleted.[;or

(iii) an altered form of structural formula (I) in which at least one of residues X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , X_8 , X_9 , X_{10} , X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , X_{16} , X_{17} , X_{18} , X_{19} , X_{20}, X_{21}, X_{22} or X_{23} is conservatively substituted with another residue].

EXHIBIT B

Claim Amendments: Pending Claims After Entry of Instant Amendment

1. An ApoA-I agonist compound comprising:

(i) a 15 to 29-residue peptide or peptide analogue which forms an amphipathic α-helix in the presence of lipids and which comprises formula (I) :

$$Z_1\text{-}X_1\text{-}X_2\text{-}X_3\text{-}X_4\text{-}X_5\text{-}X_6\text{-}X_7\text{-}X_8\text{-}X_9\text{-}X_{10}\text{-}X_{11}\text{-}X_{12}\text{-}X_{13}\text{-}X_{14}\text{-}X_{15}\text{-}X_{16}\text{-}X_{17}\text{-}X_{18}\text{-}X_{19}\text{-}X_{20}\text{-}X_{21}\text{-}X_{22}\text{-}X_{23}\text{-}Z_2$$

or a pharmaceutically acceptable salt thereof, wherein:

X_1 is Pro (P), Ala (A), Gly (G), Gln (Q), Asn (N), Asp (D) or D-Pro (p);

X_2 is an aliphatic residue;

X_3 is a Leu (L) or Phe (F);

X_4 is Glu (E)

X_5 is an aliphatic residue;

X_6 is Leu (L) or Phe (F);

X_7 is Glu (E) or Leu (L);

X_8 is Asn (N) or Gln (Q);

X_9 is Leu (L);

X_{10} is Leu (L), Trp (W) or Gly (G);

X_{11} is an acidic residue;

X_{12} is Arg (R);

X_{13} is Leu (L) or Gly (G);

X_{14} is Leu (L), Phe (F) or Gly (G);

X_{15} is Asp (D);

X_{16} is Ala (A);

X_{17} is Leu (L);

X_{18} is Asn (N) or Gln (Q);

X_{19} is a basic residue;

X_{20} is a basic residue;

X_{21} is Leu (L);

X_{22} is a basic residue;

X_{23} is absent or a basic residue;

Z_1 is R_2N- or RC(O)NR-;

Z_2 is -C (O) NRR or -C (O) OR;

each R is independently -H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl or a 1 to 7-residue peptide or peptide analogue in which one more bonds between residues 1-7 are independently a substituted amide, an isostere of an amide or an amide mimetic;

each "-" between residues X_1 to X_{23} and between residues of the peptide to Z_2 independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic; or

(ii) a 15 to 26-residue deleted peptide or peptide analogue according to formula (I) in which one or two helical turns of the peptide or peptide analogue are optionally deleted.

43. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 1, in which one helical turn is deleted.

44. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 1, in which three, four, six, seven or eight residues X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, X_{10}, X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, X_{16}, X_{17}, X_{18}, X_{19}, X_{20}, X_{21} and X_{22} are deleted.

45. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 44, in which 3 consecutive residues are deleted.

46. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 44, in which 4 consecutive residues are deleted.

47. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 44, in which two non-contiguous sets of 3 consecutive residues are deleted.

48. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 44, in which two non-contiguous sets of 4 consecutive residues are deleted.

49. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 44, in which one set of 3 consecutive residues and one set of 4 consecutive residues are deleted.

50. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 44, in which 6, 7 or 8 consecutive residues are deleted.

51. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 44, in which residues 18, 19, 20 and 22 are not deleted.

52. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 1, in which residues 3, 6, 9 and 10 are not deleted.

53. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 1, in which X_{23} is absent.

54. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 1 in which:

the "-" between residues designates -C (O) NH- ;

Z_1 is H_2N- ; and

Z_2 is -C (O) OH or a salt thereof.

55. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 1, in which the mean hydrophobic moment, $<\mu_H>$, is about 0.45 to about 0.65.

56. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 55, in which the mean hydrophobic moment, $<\mu_H>$, is about 0.50 to about 0.60.

57. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 1, in which the mean hydrophobicity, $<H_o>$, is about -0.050 to about -0.070.

58. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 1, in which the mean hydrophobicity, $<H_o>$, is about -0.030 to about -0.055.

59. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 1, in which the mean hydrophobicity of the hydrophobic face, $<H_o^{pho}>$, is about 0.90 to about 1.20.

60. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 59, in which the mean hydrophobicity of the hydrophobic face, $<H_o^{pho}>$, is about 0.94 to about 1.10.

61. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 1, in which the pho angle is about 160° to about 220°.

62. (New) The 15 to 26-residue deleted peptide or peptide analogue of Claim 61, in which the pho angle is 180° to about 200°.

63. (New) An ApoA-I agonist-lipid complex comprising an ApoA-I agonist compound and a lipid, wherein the ApoA-I agonist compound is a deleted peptide or peptide analogue according to Claim 1.

64. (New) An ApoA-I agonist-lipid complex comprising an ApoA-I agonist compound and a lipid, wherein the ApoA-I agonist compound is a deleted peptide or peptide analogue according to Claim 43, 44, 50 or 51.

65. (New) The ApoA-I agonist-lipid complex of Claims 63 or 64, in which the lipid is sphingomyelin.

66. (New) A pharmaceutical composition comprising an ApoA-I agonist compound and a pharmaceutically acceptable carrier, excipient or diluent, wherein the ApoA-I agonist compound is a deleted peptide or peptide analogue according to Claim 1 or 44.

67. (New) The pharmaceutical composition of Claim 66, in which the ApoA-I agonist compound is in the form of an ApoA-I agonist compound-lipid complex, said complex comprising the deleted ApoA-I agonist compound and a lipid.

68. (New) The pharmaceutical composition of Claim 67 in which the lipid is sphingomyelin.

69. (New) The pharmaceutical composition of Claim 67 or 68 in which the ApoA-I agonist compound-lipid complex is in the form of a lyophilized powder.

70. (New) The pharmaceutical composition of Claim 67 or 68 in which the ApoA-I agonist compound-lipid complex is in the form of a solution.